National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Acquired Immune Deficiency Syndrome

AIDS VACCINE RESEARCH WORKING GROUP

September 6, 2005

Le Centre Sheraton Montreal Hotel
1201 Boulevard Rene-Levesque West
Salon 4-5
Montreal, Quebec, Canada

Meeting Summary

The AIDS Vaccine Research Working Group (AVRWG) met in a public session on September 6, 2005 immediately prior to the AIDS 2005 Vaccine Conference in Montreal, Quebec, Canada; Le Centre Sheraton Montreal Hotel, Salon 4-5.

AVRWG members present: Barton Haynes (chair), Debbie Birx (ex officio), James Bradac (executive secretary), Susan Buchbinder, Chuck Vitek (ex officio), Karen Goldenthal (ex officio), Scott Hammer, Eric Hunter, Bette Korber, Gary Nabel (ex officio), Steven Wakefield, Ian Wilson, David Watkins, Jerald Sadoff.

Opening Remarks

Dr. Haynes welcomed participants and announced that the 2006 dates for the AVRWG meetings would be January 10-11, 2006 in Bethesda, MD; May 24-25, 2006 (changed to May 25 & 26, 2006) in Bethesda, MD; and August/September, 2006 in conjunction with the AIDS 2006 Vaccine Conference in Amsterdam, The Netherlands. Alan Greenberg has retired from the CDC and is no longer and ex-officio member. For this meeting Chuck Vitek will serve as the CDC representative. Emilio Emini has resigned from AVRWG upon accepting a position at Wyeth Pharmaceuticals. Several reorganizations have taken place at the Division of AIDS, Joseph Chiu is now serving as the Acting Branch Chief for the Vaccine Clinical Research Branch, and Jorge Flores has moved to Deputy Director of the Vaccine & Prevention Research Program under Director, Peggy Johnston. We will hear from a Preclinical update from Jim Bradac today and have a clinical update from Joseph Chiu at the next AVRWG meeting in January, 06.

AVRWG Report 2006

It was decided that the committee draft an AVRWG 2006 Report to the Division of AIDS/NIAID with recommendations on the subsequent scientific areas of importance. (The VRC, CHAVI, and GHAVE should not be included in the report.) In the past this report has proven to be very useful to NIAID and has generated critical internal discussions and served as a guide in future planning.

Dr. Haynes asked that the AVRWG members assigned to assist with the report should list bullet points of the 3 to 5 top priorities in each scientific area including status and progress of the area, as well as recommendations to DAIDS/NIAID for fine-tuning programs. Dr. Haynes will then put together and executive summary for submission to NIAID.

Reports from each member below are due to Bart Haynes by October 1, 2005. The draft summary report should be completed by November 1, 2005, and the final report submitted to DAIDS by December 15, 2005.

The AVRWG 2006 Report Outline and Assignments are as follows:

Clinical Trials	Scott Hammer/ Susan Buchbinder (asst.)
Correlates of Protection & Animal Models	David Watkins
T cell responses & Immunogens	Bette Korber
B cell responses & Immunogens/ Structural Aspects of gp120 & gp41	Montefiori/ Ian Wilson
Neutralizing Antibody Responses	Joe Sodroski/ Haynes & Montefiori (asst.)
Social Economic & Ethical Issues	Steve Wakefield/ Susan Buchbinder (asst.)
Innate Immunity & Adjuvants	Larry Corey
Vector Development for long lasting mucosal immunity	Eric Hunter

DAIDS Programmatic Update- James Bradac, Ph.D., DAIDS

The AVRWG members will find in their folders the following items: a Preclinical Research and Development Branch Vaccine Production Milestone table, a listing of FY05 grant and contract awards (including the CHAVI award) with brief summaries of each, the summary of the 2005 January and May AVRWG meetings, the summary of the Novel Technologies for Evaluating Cellular Immune Responses in Nonhuman Primates meeting (organized by Jeffrey Ahlers: DAIDS) held October 25, 2004.

Regarding FY05 grant awards, there was a recommendation that the AVRWG should look at which awards were not made and why, as well as the number of proposals received and the percentage of those that were funded. The HIVRAD and IPCAVD have a 40 % and 50% funding rate respectively. This is a more successful ratio that in years past and it seems that investigators have addressed reviewers' suggestions and received better scores.

Four new HIVRAD Program Project grants were awarded to: David Knipe (Herpesviruses as Vaccine Vectors for AIDS), Chris Miller (Mechanisms of Protection in Live-attenuated AIDS Vaccine), Bob Whalen (Development of Novel Immunogens for Vaccine to HIV-1) and Barton Haynes (Centralized HIV-1 Genes as Vaccines). One IPCAVD cooperative agreement grant was awarded to Dan Barouch (Novel Adenovirus

Vector-Based Vaccines for HIV-1). Two HVDDT contract awards were made to Children's Research Institute-Philip Johnson (rAAV vectors), Chiron Corporation- Susan Barnett (rAlphavirus vectors). One CHAVI award was made to Barton Haynes at Duke University with a Scientific Leadership Group whose members include Andrew McMichael, Joseph Sodroski, George Shaw and Norman Letvin.

Dr. Bradac gave a brief history of the Innovation Grant program and explained the new Phased Innovation Award Program (PIA) that will use the combined R21/R33 mechanism. The R21 portion will be eligible to receive 2 years of funding and proceed to an R33. If milestones are met, and the R33 portion awarded, it will then be phased into a 5 year grant. Grants will be kept budget neutral and it is anticipated that approximately 50% of R21's will be eligible to roll into R33's. The NIH wide Program Announcement is expected to be released in May, 2006.

Action Item: It was requested by Dr. Peggy Johnston, that Dr. Jon Warren as the PIA Director to provide the AVRWG with an assessment of the anticipated R21/R33 awards to be made under the new PA.

Dr. Bradac noted that since the AVRWG vector workshop held in January, 2005 the following vector related projects have been initiated: R01- M. Schnell, Rabiesvirus vectors; HIVRAD- David Knipe, HSV vectors; IPCAVD- Dan Barouch, rAd vectors, HVDDT- CRI (rAAV), Chiron (rAlphavirus); Preclinical Master Contract (ABL), M. Robert-Guroff, rAd; SVEU- H. Naim, rMeasles virus, R. Andino rPoliovirus.

Dr. Bradac assured Dr. Sadoff and AVRWG members that the role of the Preclinical Research & Development Branch within the Vaccine Program is to monitor grantees and contracts while keeping up with the innovative advances that are progressing in industry. PRDB staff understands the amount of effort it takes to oversee all grants and contracts that manufacture products for testing in humans. PRDB continues to preserve its work with other promising scientific advances in the field.

Overview of AIDS- related to Grand Challenges in Global Health-
Nina Russell M.D., Bill & Melinda Gates Foundation

Dr. Russell presented history of the origins of the Grand Challenges, beginning with David Hilbert's devotion to solving mathematics in1900 to Bill Gates inspiration by Hilbert's approach, in 2003 to generate a scientific board to elicit ideas from the world community to define the "grand challenges" in global health and fund research to solve these problems.

A Grand Challenge is a call for specific or technological innovation that would remove a critical barrier to solving an important health problem in the developing world with a high likelihood of global impact and feasibility. It is not a statement of the global health problem itself, or the request for a specific health intervention.

The essence of Grand Challenge is to focus on solutions. These are driven by milestones

and deliverables and geared toward a plan for success. 14 Grand Challenges target 7 global health goals including: improvement of childhood vaccines, creation of new vaccines with a call to devise, design and learn, control of insects that transmit agents of disease, improvement of nutrition of promote health, improvement of drug treatments for infectious diseases, cure latent and chronic infections, and measure disease and health status accurately and economically in poor countries. Toward these 14 Grand Challenges, over the Gates Foundation received over 1,500 letters of intent, 445 proposals were invited to be submitted, and 406 were received. Funding for awarded Grand Challenges began in July, 2005.

The Grand Challenge awards have a priority area that includes HIV. Most of those associated with HIV/AIDS fall under the second long term goal which is to Create New Vaccines. Each Grand Challenge assesses the background known on the specific challenge, roadblocks associated with it, major challenges seen, potential benefits, and specific diseases that are priority areas.

- Awarded under Grand Challenge #4: To devise reliable tests in model systems to evaluate live-attenuated vaccines; PI- R. Flavell "A Mouse Model to Evaluate Life-Attenuated Vaccine Candidates"; PI- R. Balling "Novel Mouse Models for Testing HIV and HCV Vaccines"; PI- H. Deng "Development of Novel Mouse Models for HIV and HCV Infection."
- Awarded under Grand Challenge #5: Solve how to design antigens for effective, protective immunity; PI-R.J. Shattock "Novel Antigen Design and Delivery for Mucosal Protection Against HIV-1 infection".
- Awarded under Grand Challenge #6: Learn which immunological responses provide protective immunity; PI- F. "Plummer Comprehensive Studies of Mechanisms of HIV Resistance in Highly Exposed Uninfected Women"; PI- G. Shaw "Molecular Analysis and Modeling of HIV-1 Transmission, Containment, and Escape."
- Awarded under Grand Challenge #12: Create immunological methods that can cure chronic infections; PI- D. Baltimore "Engineering Immunity Against HIV and Other Dangerous Pathogens."

The scientific team assembled to administer the Grand Challenges, serve as Program Officers and interact as a separate entity from the Global HIV/AIDS Enterprise. During the review of the proposals, the team looked for structure, milestones and deliverables as well as a goal for a global strategy. This was a new way of approaching grants and took investigators and immense amount of time to structure their grant under the specific parameters given. Regarding intellectual property issues, the projects vary with large consortia of partnerships, but the goal is to remain consistent in insuring access of their product to the global world.

Global HIV/AIDS Vaccine Enterprise-
Jose Esparza, Ph.D., M.D., Bill & Melinda Gates Foundation

An HIV Vaccine Enterprise was developed in response due to the severity of the AIDS pandemic plaguing the world's population. An HIV Vaccine is one of the major scientific

challenges faced today and the current efforts to develop an HIV vaccine have so far proven to be insufficient. The Enterprise was formed to renew the effort that is needed for the development of a safe and efficacious HIV vaccine.

The development of the Enterprise was conceived in the 2003 Proposal in "Science" magazine, which followed with a development of a scientific plan, (published in January, 2005) and received political endorsement at the 2004 G8 Sea Island summit and further endorsement at the 2005 G8. The Scientific Strategic Plan was developed through a process of consultation involving 140 scientists representing 17 countries around the world.

The Enterprise seeks to speed development of an effective HIV vaccine by prioritizing, direction resources, development, manufacturing and testing, implementing common standards to comparatively assess results, and maximizing the sharing and use of data. The Enterprise is not proposing to replace the creativity of the individual investigator, but is creating a new way to think about problems, a new way of acting to solve problems and a new way of behaving as a global community of problem-solvers. Sharing information and maintaining a correct balance between collaboration and competition is critical to the success of the Enterprise.

Areas of scientific importance to the Enterprise include but are not limited to: vaccine discovery, laboratory standardization, product development and manufacturing, clinical trials capacity, regulatory considerations and intellectual property issues.

- The Vaccine Discovery group has two goals, one of which is to research the design of novel immunogens that induce potent, broadly reactive, persistent neutralizing antibodies. The other is to design novel (T-cell) immunogens that suppress viral replication and prevent escape of virus from immune control.
- The Laboratory Standardization group plans to compare results from preclinical and clinical trials and focus on additional collaborative projects.
- Aiming to close the gap between existing global capacity and future requirements for conducting clinical trials is the focus of the Clinical Trials Capacity group.
- The Product Development and Manufacturing group will assist in identifying and/or establishing a dedicated HIV vaccine bioprocess and analytical development group(s) including supporting vaccine discovery centers, providing training and building, acquiring, or contracting manufacturing facilities.
- Regulatory Considerations would like to ensure expeditious, high quality review and decision making by regulatory authorities in all aspects of developing, testing and manufacturing a potential vaccine.
- The Intellectual Property group focuses on creating an IP framework that facilitates and "enabling environment" and fosters stronger collaboration, data sharing, and use of common materials and reagents in the field.

The Enterprise is not an organization yet has an organizational structure to foster networking and collaborations. They are currently in the process of recruiting a permanent secretariat while Jose Esparza continues to serve during the interim. The secretariat will monitor, update and implement the scientific plan as well as serve as an

advocate for political support and expand the Enterprise partnership.

Dr. Esparza presented the Request for Proposals (RFPs) from the Gates Foundation that included Centers or Consortia on Vaccine Discovery, specifically antibody-inducing products (VDAC) and T-cell-immunity-inducing vaccines (VDTC), as well as Vaccine immune-monitoring, specifically laboratory standardization (VIMC). The RFP's have a funding total of $360M for 5-6 years. The RFPs were developed to add value to the HIV/AIDS research field and are not intended to duplicate ongoing activities in other centers. Gates does not intent to add additional money to already well-funded areas. The goal of the RFPs was to fund new innovative ideas that have little or no funding.

The Gates Foundation serves a portion of the Enterprise network and fosters interaction between all partners. The HIV Vaccine Enterprise consists of a global community dedicated to the discovery of an HIV vaccine. These partners include: CHAVI/NIH, ANRS, Gates Foundation, IAVI, EDCTP/EC and many others that are committed to the global epidemic.

Dr. Wakefield wanted to be sure that the Enterprise fosters social and political support for the administration of clinical trials that show promising results as part of a developing nation's national plan. He would also like to know the agenda of the Enterprise, in assisting developing nations to create a national plan to conduct clinical trials. Dr. Esparza responded by stating that the Enterprise has recently been focused on the science in the field but plans to develop a conclusive environment to better foster these relations and national plans in developing countries. He also add that currently 19 people serve on the Enterprise committee and that with the appointment of a secretariat the final shape and structure of the Enterprise will develop and include this issues.

Dr. Katharine Kripke raised the question of why it took researchers and scientific administrators 20 years to propose a group such as the Enterprise to change the culture in the ways AIDS research was done. Dr. Esparza responded that the idea for the Enterprise was realized in 1993 when scientists saw that the problem of HIV/AIDS was going to require a different infrastructure and a change in culture. A mechanism was needed to foster a cultural change and call for more collaboration rather than competition. The Human Genome project served as a model for the development of the Enterprise.

The Center for HIV/AIDS Vaccine Immunology (CHAVI)-Barton Haynes, M.D., Duke University School of Medicine

Dr. Haynes, as the principal investigator of the CHAVI award, presented on the organization, preliminary scientific plans, functionality, measurements of success and timelines planned for this new virtual center.

The Scientific Leadership Group Projects consist of: Dr. Norman Letvin, who plans to look at the correlates of SIV/SHIV protection in non-human primates-mucosal challenge; Dr. Andrew McMichael who will study correlates of protection in exposed and uninfected subjects; Dr. George Shaw who will look at neutralization properties of

transmitted HIV-1 and Dr. Joe Sodroski who will work to elucidate the structure of the transmitted virus trimer.

In Year 01, there will be various Cores that will specifically focus on: host genomics and viral genetics, the CHAVI clinical sites for the study of HIV-1 transmission, vector development, structural biology and clinical trails. The CHAVI website now resides on the Duke University server and more information regarding CHAVI can be found at www.chavi.org.

The clinical study sites for year one are all sites that are functioning now. The goal is to duplicate efforts that are ongoing as little as possible. CHAVI sites include Malawi, Johannesburg and Durban South Africa, Uganda, Tanzania, Zambia, London and University of California San Francisco.

The overall goals of CHAVI are:

1. To elucidate early viral and immunological events and host genetic factors associated with HIV-1 transmission, establishment of productive infection, and (partial) containment of virus replication.
2. To determine correlates of SIV immune protection in primates
3. To design, develop, and test novel immunogens and adjuvants that elicit persistent mucosal and/or systemic immune responses in humans and primates
4. To evaluate HIV-1 vaccine candidates in early phase clinical trails.

CHAVI has four specific aims to further study early acute HIV-1 infection in patients. Study populations include acutely HIV infected patients (all prior to seroconversion), exposed and uninfected subjects, chronically infected subjects, acute infections will be detected by screening subjects presenting to STD clinics. These efforts are lead by Dr. Myron Cohen with support from Family Health International. Plans include looking at approximately 500 acutely infected and 250 chronically infected individuals.

The discovery phase of work will continues from years 1 to 5, with the translational product development phase of work beginning in year 2 through year 7. There are also plans to eventually study mother to child transmission issues in the out years. CHAVI plans to bring in new discovery teams after year one and will make HIV-1 sequence and epitopes available to the HIV research community. CHAVI wants to maintain accessibility and interaction with the HIV community as per the Global HIV/AIDS Vaccine Enterprise strategic plan.

CHAVI will measure success by its ability to work together, work quickly, perform critical experiments that help drive the field, perform adequately powered ‘large’ science, perform risky science and to have failures. CHAVI will also be successful if the center experts are able to define the viral and host events at systemic and mucosal sites in very early AHI, discover the correlate of immunity in all protective genes or predisposing genes for HIV-1 infection or disease, test the best adjuvants (plans to work with the VRC), perform Phase I trials to iteratively inform vaccine discovery and development.

The most recent CHAVI Organizational Meeting took place several weeks ago, August 23-25, 2005 in Durham, NC. This meeting outlined IP, legal, compliance, IT, management and operations, roles of NIH staff, scientific directions, subcontracting and the implementation of a timeline from September 2005-February 2006. By the first part of 2006 CHAVI plans to begin prospective enrollment for screening of the EU.

There is a 120 page agreement covering IP issues, cooperative agreements, specimen shipping, material transfer agreements, discoveries, licensing, etc. Amendments to this document are currently ongoing. CHAVI specifically selected robust sites from the NIH and their networks, which have already addressed IRB and ethical issues. Dr. Korber suggested holding satellite meetings to discuss developing issues on a site by site basis, as each country varies and has diverse populations. This will develop an international framework for CHAVI's leadership.

Dr. Sadoff suggested taking what is known about the HIV/AIDS disease and studying the high attack rates at various sites. He would like to see researchers do something different at a new site rather than repeat what was done at the last site that failed. A new paradigm is needed. He encouraged scientists not to look at long term non-progressors, but to tie a clear strategy to the vaccines being put into field sites. Dr. Johnston stated that this is a behavioral infection and intervention and STDs must also be considered. Dr. Nabel stated that Dr. Sadoff's suggestion as a possible direction in designing a Phase III study.

Announcement: Dr. Johnston announced Dr. Haynes will rotate off as Chair of the AVRWG, and Bette Korber will rotate off as well. This will take place at the next meeting in January, 2006.

The meeting adjourned at 5:15pm.